REMARKS

Applicant has made several modifications to Claim 1 and several dependant claims and added new claim 43 to address and tee-up the differences between Applicant's invention and the Examiner's proposed combination of Cialdi '741; Renier '978; della Valle '521; Sirhan '679; and Valentini '205. Applicant has also added claims 44 (independent), 45-54 (dependent) which are similar to the previously pending claims and are discussed in conjunction with the previously presented claims. For the reasons discussed below, the presently pending claims are patentable over the Examiner's proposed combination.

Discussion of the Proposed Combination

According the Examiner:

1. Cialdi '741 discloses a device having a coating of sulfate polysaccharide wherein the polysaccharide is hyaluronic acid (HA). Cialdi also discloses adding a pharmacologic drug can be administered in association with the drug. Applicant also notes that Cialdi teaches away from producing a hyaluronic acid polymer coating wherein the ester derivative of hyaluronic acid is not sulfated, that is, he specifically advocates sulfated polysaccharides, "The sulfation of alcoholic hydroxyls present in the polymeric chain of a polysaccharide or of one of its semisynthetic derivative by the use of a suitable sulfating agent can lead to the formation of new derivatives with chemical physical characterizes, but most of all biological characteristics, which are different from those of the starting material. Sulfation of such preprocessed biomaterial is a novel features of the present invention." See Column 2, lines 29-49. The reagents commonly used for sulfation include the complex between sulfur trioxide and pyridine (SO_3-pyridine). Col. 2, lines 61-63. Also see Col. 3, lines 5-25.

2. Renier '978 discloses a biomaterial (such as a stent) that has sulphated hyaluronic acid compounds and esters.

3. Della Valle '521 discloses that certain HA esters may have certain types of carboxylation. Applicant also observed that in table 1, Della Valle gives the activity levels of 9 hyaluronic esters of cortisone, hydrocortisone, and flurocortisone. (numbered HYC1-HYC9). Col. 36, line 60-65.

Six of the derivatives (HYC1-HYC3, HYC7-HYC9) were dissolved in saline, and three (HY4-HY6) were dissolved DMSO. Col. 37, lines 20-25. All nine of the HYAC's were effective in producing antiinflammatory response, but the most efficient of these derivatives were HYC4-HYC6, the one dissolved in DMSO, *i.e.* the ***sulfated ones.*** Col. 37, lines 40-50.

4. Sirhan '205 discloses a stent for delivering a matrix 40 having a therapeutic agent 28. Sirhan also discloses the use of a rate controller element 43 to adjust the release rate of the agent, and discloses a release rate for the drug from 1-200 days. The rate controller element 43 is attached above the matrix, see figure 2G.

5. Valentini '205 discloses an implant with a polystyrene coating which can be applied by dipping or spraying. In example IV, Valentini discloses circular films of HYAFF (HA benzyl ester films). Valentini states, "Cells were seeded on GRDGS-coupled films, CD1-activated films, and on standard tissue culture polystyrene wells." Col. 12 line 56-57. The results of the tests showed that tissue growth was greatest in the polystyrene wells.

The Invention of Claim 1 (and 44)

Claim 1 requires a double coated stent comprising a first and second coating, wherein the first coating contains a polymer of hyaluronic acid and a first quantity of a pharmacologically active ingredient. The second coating is a hydrophobic polymer beneath the first coating also containing the pharmacologically active ingredient. Both of the coatings act as reservoirs for the pharmacologic agent.

None of the references cited by the Examiner, alone or in combination, disclose a doubled-coated stent wherein both coatings act as "reservoir." The closest reference the Examiner cited is Sirhan which discloses a stent having a matrix 40 supporting a therapeutic agent 28 and a rate controller element 43. While the matrix and the controller element could possibly be described as coatings, they do not meet the features of the claim because they do not both function as reservoirs for the same active ingredient. They also do not have the claimed thickness, *see* Claim 43 for example. The primary reference on which the Examiner relied was Cialdi '741, which only discloses a one HA polymer coating for a device (the hydrophobic coating is not disclosed).

There appears to be a mistake in Office action on Page 10. The Examiner states, "The above mentioned prior art also fails to teach the thickness of the polymer coating. Since the above art teaches the stent of instant claim 1 with limitations of claim 21, it would[ha]ve been *prima facie* obvious to one of ordinary skill at the time the invention was made to determine the optimum thickness of the HA polymer coating that would be the most effective." No where in section 7 (starting on page 9 of OA) does the Examiner form a combination of a stent which has two coatings as was previously claimed in previous claim 21. As explained above, all 5 cited references discloses a single coated medical device for delivering a pharmacologic agent.

The present invention utilizes *a double coated design.* Moreover, the double coating design allows for the modulating of the release of the active ingredients and extends their pharmacological action over time; in this way, the therapeutic effects at the lesion site can be prolonged according to the release time of the second coating which adds to the release time of both the active ingredient and the hyaluronic acid contained in the first coating. This design, for example, allows for a fast dissolving coating to be stacked with a slow dissolving coating to provide high levels of active ingredient and then lower levels of agent for a longer period of time. Also providing a hydrophobic coating enhances adhesion of the first coating to the stent.

None of the single coating designs of cited examples 1-5 disclose a double layered stent as claimed and Claim 1 is patentable over them alone or in combination. Claim 44 is patentable for substantially the same reasons.

Claim 8 (and 45), Non-Sulfated Ester Derivative of Hyaluronic Acid

Previously pending Claim 1 included a feature requiring the ester derivative of hyaluronic acid to be not sulfated. The Examiner sought to combine Cialdi, Renier, and Della Valle. The Examiner admits that Renier asserts a sulphated hyalronic acid (OA, page 6), so whether or not Cialdi is combined with Renier or not is not relevant to whether the combined product discloses a not-sulfated ester derivative of hyaluronic acid. Della Valle demonstrates that sulfated HYAC's (one dissolved in DMSO) are better at creating an antiinflammatory response. Col. 37, lines 40-50. Moreover the base reference (Cialdi) goes to great length to explain how sulphation is key to the invention. Sulphation of polysaccharides is a fundamental aspect of the Cialdi

invention. See Columns 2-3 generally, as an example, the Examiner is directed to review the first sentence of the second, third, forth, and fifth paragraphs. The Examiner's sweeping remark that sulfated and non-sulphated HA esters are functional equivalents is respectively traversed, because it is not accurate nor is it substantiated by the evidence (patents) presented by the Examiner. On the contrary, both of the references provided by the Examiner teach that sulfated polysaccharides "increase blood coagulation time" (Cialdi) and the "HYC (hyaluronic acid esters of cortisone) derivatives all proved to possess a considerable antiinflammatory activity consistently superior to that of the corresponding cortisones tested in parallel, [but] the most efficient of these derivatives seem to be HYC4, HYC5, HYC6 (the sulphated HYC's)." The prior art clearly and unambiguously teaches sulphating a medical compound increase its ability to heal injured tissue. As a result, the Examiner has provided no evidence which would suggest that a non-sulphated ester of hyaluronic acid is obvious. More accurately, the Examiner's evidence teaches that sulfated esters of hyaluronic acid are superior to non-sulfated esters of hyaluronic acid, and so there is motivation to form the combination proposed by the Examiner.

Casting Applicant's specification and claim aside, the question is "Would one having ordinary skill in the art having read only Cialdi and Della Valle have been motivated to desulphate the sulphated esters of hyaluronic acid disclosed by Cialdi?" Clearly not. If anything, Della Valle confirms Cialdi's conclusions that sulphated hyaluronic acid work better. Col. 37, lines 41-50. "The degree of sulphation that can be obtained directly on the biomaterial is an important characteristic, and requires careful kinetic control." Col 2, lines 50-52. Della Valle's findings specifically contradict the Examiner's assertion that sulphated and not-sulphated hyaluronic acid are functional equivalents. For all these reasons, it is respectfully asserted that one having ordinary skill in the art would not have been motivated to modify Cialdi, and allowance of Claims 8 (and 45) is respectfully requested.

Claim 20 (and 46) Triple Layer Design

Claim 20 specifies a triple coating configuration by adding a middle layer of covalently bound hyaluronic acid in between the first and second coating (see figure 3 for an illustration.) Should the first coating degrade before the second coating, adding the middle layer of covalently

bound hyaluronic acid serves to protect the vessel wall from being exposed to the second coating. Exposure to the second coating can cause damage to the vessel walls. See Page 22 of the Specification. None of the references cited by examiner suggest providing a stent having a first and second coating with a middle layer of covalently bound HA between them.

When installed in a patient, the biodegradable coating of the hyaluronic acid ester polymer is in contact with the external environment. Once the first coating degrades, the hydrophobic coating may become exposed to the vessel wall, which will harm the vessel wall. To prevent this, an intermediate monomolecular layer of hyaluronic acid may be interposed thus covering the hydrophobic layer, which monomolecular layer is covalently (*i.e.* firmly) bound to the hydrophobic layer. Thus, even if erosion does occur to the hyaluronic acid ester polymer coating (the first coating) of the surface, the hydrophobic coating is not directly exposed to the vessel wall. None of the cited examples 1-5 disclose providing adding a middle layer of covalently bound hyaluronic acid in between the first and second coating and allowance of Claim 20 (and 46) is respectfully requested.

Polystyrene Claim 25 (and 47)

The Examiner addressed the features of Claim 25 on page 10 of the Office action. The Examiner noted references 1-4 did not disclose polystyrene as a preferred material for the second coating, and looked to the teaching of reference 5, the Valentini '205 patent. In columns 12-13 (EXAMPLE IV) Valentini compares the results of seeding endothelial cells on a HYAFF control film, HYAFF-GRGDS coupled film, HYAFF-GRGDS coupled film + CD1-activated films, and on standard tissue culture polystyrene (PS) wells. Col 12:37-63. The polystyrene wells that Valentini is referring to are the hard plastic laboratory equipment that lab technicians use. See for example Costar Clear Polystyrene 96-Well Plates on Amazon.com http://www.amazon.com/Costar-Polystyrene-96-Well-Untreated-Sterile/dp/B001CLNYJK or Simport's T100-6 featuring polystyrene wells http://www.simport.com/products/deep-well-plates-and-cluster-tubes/deep-well-plates/t110-6-bioblock.html. (Attached in the IDS). These wells can used use for serial dilution, hemagglutination, or precipitation assay for example (See the Amazon advertisement.) In addition to well plates for laboratory equipment, polystyrene is

used for disposable silverware (plastic cutlery), CD and DVD cases, yogurt container, and foam drinking cups.[1]

The incorporation of polystyrene into a piece of laboratory equipments used for serial dilution, hemagglutination, or precipitation assay would not provide motivation for one having ordinary skill to first figure out make a polystyrene coating, and then to place it on a vascular stent. Moreover, Valentini certainly does not suggest making a coating out of polystyrene, rather he was using the well plates to test the effectiveness of GRGDS coupled films. For all these reasons, Claim 25 is separately patentable over the art of record.

As a result, Valentini's disclosure of polystyrene is simply not relevant to the claimed invention for references 1-4. Claim 47 is patentable for similar reasons.

Linking Delivery Length and Coating Thickness

Claims 43, 18, 21, 30, 16, 22, and 29 (and Claims 48-54)

As set forth in new Claim 43, an important design configuration in developing the invention was to design an apparatus that could deliver the pharmacological active ingredient over a period of two months or more. While Sirhan '205 does disclosed degradation window of 1 day to 200 days, he provides this degradation time for a totally different type of drug delivery device. Sirhan's stent uses a single coating matrix 40 in combination with a rate controlling element 43 to achieve these times. Applicant's invention does not use a rate controlling element, rather applicant uses two coatings to achieve the claimed delivery time. In addition, Sirhan's matrix is not made of HA, is not a dual coated stent as claimed, nor does it contemplate a sequential degradation technique as provided in Claim 21. Sirhan does disclose the rate controlling element can be hydrophobic, but he does not disclose it is *beneath* the first coating (*i.e.* matrix 40), Sirhan has it the other way around (*i.e.* hydrophobic layer 43 is above matrix 40.). Moreover the rate controlling element 43 does not deliver pharmacologically active ingredients as required by Applicant's claimed second coating.

Part of the reason Applicant selected HA and polystyrene as preferred construction materials for the coatings was to develop a double coating which had a combined thickness of

[1] *See* Wikipedia under polystyrene.

about 20 microns, which could deliver pharmacologically active ingredients for a period of about two months wherein the first coating degrades before the second coating, and each coating has about the same thickness. The particular "thinness" of the coatings allows the stent to placed in smaller arteries or veins. Sirhan does not disclose what thickness of the matrix would be appropriate to create a specific delivery time, because the thickness of the matrix does not control the degradation rate in Sirhan. Rather, the rate controlling element is responsible for this feature. [0046 Sirhan]. Sirhan does not disclose the thickness of the rate controlling element 43 nor is the thickness of the matrix disclosed. New Claim 43 links the thickness and degradation times, and is patentable over references 1-5 for all of the above reasons.

Applicant has also claimed in claims 18 and 30 that each coating can last at least a month before completely degrading in the body. In addition, Claim 21 specifies that the first and second coatings deliver a controlled release of the active ingredient over a period of two months. In this configuration, the first coating (the one made from HA) degrades first, and the second coating (the hydrophobic coating) degrades second. The coating thickness of the first coating is claimed in claim 16, the middle layer claim 22, and the second coating claim 29.

The Examiner's design choice rejection page 10-11 relating to the assertion that one having ordinary skill the art could simply determine what thickness would be optimal fails to account for the large differences in uses amongst the many different medical devices he seeks to combine. None of the references cited provide sufficient information for one having ordinary skill in the art to determine that approximately 10 microns for both the first and second coatings provide a delivery period of about two months. This is especially true for Sirhan who arrives at the desired delivery period by changing the rate controlling element as opposed to the thickness of the coating. For all these reasons, the Examiner's proposed combination does not disclose Claims 43, 18, 21, 30, 16, 22, and 29. Claims 48-54 are patentable for similar reasons.

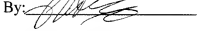
CONCLUSION

In light of the above remarks, reconsideration and withdrawal of the outstanding rejections are specifically requested and it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Payment of the fee for a 1 month extension is submitted with the response. No only fees are believed due; however, the Commissioner is authorized to charge any fees due in connection with the filing of this response to our Deposit Account No. 50-1349. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for in the enclosed transmittal, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: October 19, 2010

By: 

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